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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/499,006	02/04/00	BAGGOT	D 249/127

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EXAMINER	
JOHANNSEN, D	
ART UNIT	PAPER NUMBER
1655	7

DATE MAILED: 06/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/499,006	Baggot
Examiner	**Art Unit**
Diana Johannsen	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 4, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

FINAL ACTION

1. This action is in response to paper no. 6 filed April 4, 2001. Claims 1-11 have been amended and claims 12-14 have been added. Claims 1-14 are now pending. The amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 U.S.C. § 112

3. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons stated below and in the Office action of paper no. 5. **It is noted that Applicant's amendments to the claims necessitated the new grounds of rejection set forth below and the inclusion of claims 12-14 in this rejection.**

Claims 1-6 are indefinite for failing to recite a final process step that clearly relates back to the preamble. It is noted that the claims have been amended such that they are now drawn to a "method of treating a chromosomal abnormality". However, the final step of the claims merely requires "prescribing a biochemical treatment" for any metabolite that differs from "the normal level of that metabolite". The claims as written never make clear how one would conclude that a

chromosomal abnormality is present, or make clear whether this is even necessary (i.e., are the claims intended to be drawn to a method of prescribing a treatment for any patient having an abnormal level of any metabolite [as the final process step suggests], or are the claims limited to treatment of a fetus with a chromosomal abnormality [as the language of the preamble suggests?). It is noted that the claims have also been amended to include a step of "generating a biochemical characterization of the chromosomal abnormality in the fetus, wherein the characterization comprises a list of each of the plurality of metabolites of the patient profile". However, this language suggests that any list of metabolites from any type of patient -- including a list of metabolites which are all present at normal levels -- would constitute a "biochemical characterization" of a "chromosomal abnormality". Accordingly, the claims should be amended so as to clarify how the recited method steps would result in treatment of a "chromosomal abnormality in a fetus".

Claims 1-7 and 12-13 are indefinite over the recitation of the language "prescribing a biochemical treatment for each [respective] metabolite" in claims 1 and 7, for the reasons stated in the Office action of paper no. 5. It is unclear as to what is meant by this language. Specifically, it is unclear as to whether this language is intended to suggest that a treatment is to be prescribed for, e.g., a fetus or a mother, or whether one is to actually "prescribe a treatment" for a "metabolite". Further, it is unclear as to what might be encompassed by the language "biochemical treatment". The response does not traverse this rejection.

Claims 7 and 12-13 are indefinite for failing to recite a final process step that clearly relates back to the claim preamble. It is noted that the claims have been amended such that they are now drawn to a "method of performing a comprehensive biochemical analysis of a specimen of bodily fluid from a patient in order to treat Down Syndrome in a fetus". However, the final step of the claims merely requires "prescribing a biochemical treatment" for any metabolite that differs from control levels. The claims as written never make clear how such prescribing relates to treatment of Down Syndrome. For example, how would one determine that Down Syndrome is present, and is this intended to be a part of the claimed method? The claims should be amended so as to clarify how the recited method steps would allow one to accomplish treatment of Down Syndrome.

Claims 8-11 and 14 are indefinite for failing to recite a final process step that clearly relates back to the claim preamble. It is noted that the claims have been amended such that they are now drawn to a "method of characterizing the levels of a plurality of metabolites that are present in a fetus with a chromosomal abnormality", and that the claims recite a final process step of "analyzing" a patient profile with respect to an abnormal profile. However, the claims now require that the "abnormal profile" be representative of "patients suffering from Down Syndrome". Accordingly, it is unclear as to whether the claims are intended to be drawn to methods of "analyzing" a patient profile relative to a patient with Down Syndrome, or to methods of "characterizing" a fetus with any chromosomal abnormality. Clarification is required. Further, the claims remain indefinite over the recitation of the term "characterizing" in the present claims,

for the reasons stated in the Office action of paper no. 5. For example, what actual information would have to be detected or gathered to accomplish "characterization"?

Claims 1-6 are indefinite over the recitation of the phrase "measuring the level of each metabolite in the specimen" in claim 1. It is unclear as to whether the language "each metabolite" is intended to refer back to the "plurality of metabolites" previously recited in the claims, or whether this language is intended to indicate that the level each and every metabolite in the specimen must be measured. Clarification is required.

Claim 5 is indefinite because it is unclear as to how the claim would limit claim 1, from which it depends, if the recited differences relative to "the control profile" are non-existent. Clarification is required.

Claims 7 and 12-13 are indefinite over the recitation of the phrase "the abnormality of the fetus", "the respective enzyme", and "the enzyme activity for a metabolite" in claim 7. There is insufficient antecedent basis for these limitations in the claims.

Claims 7 and 12-13 are indefinite over the recitation of the phrase "if the enzyme activity for a metabolite of the patient profile is high/low relative to the level of that metabolite in the control profile" in claims 7 and 12-13. It is unclear as to whether this language is intended to indicate that "prescribing" is to occur only if differences are detected in enzyme activity levels and/or if differences are detected in metabolite levels. Clarification is required.

Claim 12-13 are indefinite because it is unclear as to how the claims would limit claim 7, from which they depend, if the recited differences relative to "the control profile" are non-existent. Clarification is required.

Claims 14 is indefinite because it is unclear as to how the claim is intended to further limit claim 8, from which it depends. First, it is noted that claim 8 is drawn to a method of "characterizing", whereas claim 14 requires "prescribing". Thus, it is unclear as to whether the method of claim 14 has a different objective from that of claim 8 (e.g., treatment), or whether the requirement for "prescribing" is intended to contribute to "characterization". Second, it is unclear as to how claim 14 would limit claim 8 if the recited differences relative to "the abnormal profile" are non-existent. Clarification is required.

Claim Rejections - 35 U.S.C. § 103

4. In view of the amendment of claim 4 such that the claim is drawn to a method of treating a chromosomal abnormality in a fetus that requires determining if the levels of formiminoglutamic acid, homocysteine, normetanephrine, oxalic acid, serine, and tetra-hydro-biopterin in a "bodily fluid from a patient" differ from a control as recited in the claim, the rejection of claim 4 as being unpatentable over Hoffmann et al (Clin. Chem. 35(4):587-595 [4/1989]) in view of Galjaard (Ballieres Clin. Obst. Gyn. 1(3):547-567 [9/1987]) is withdrawn.

5. In view of the amendment of claim 7 such that the claim is drawn to a method of "performing a comprehensive biochemical analysis of a specimen of a bodily fluid from a patient in

order to treat Down Syndrome" in which metabolites are analyzed and "activity level for an enzyme" is determined for each metabolite, the rejection of claim 7 as being unpatentable over Hoffmann et al in view of Galjaard is withdrawn.

6. In view of the amendment of claim 8 such that the claim is drawn to a method of "characterizing the levels of a plurality of metabolites that are present in a fetus with a chromosomal abnormality" in which metabolite levels in amniotic fluid are compared to a metabolic profile from a Down Syndrome patient, the rejection of claims 8-11 as being unpatentable over Hoffmann et al in view of Galjaard is withdrawn.

7. Claims 1-3 and 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffmann et al in view of Galjaard, for the reasons stated below and in the Office action of paper no. 5.

The response traverses the rejection on the following grounds. The response states that the claims "are directed to methods for characterizing the levels of a plurality metabolites in an amniotic fluid sample relative to the levels of those metabolites in a control profile in order to treat an chromosomal abnormality in a fetus". The response notes that 'A chromosome contains a plurality of genes control a plurality of enzymatic activities", and that "to treat a chromosomal abnormality, such as, e.g., Down Syndrome, the present claims are directed to methods of generating and analyzing a profile of a plurality of metabolites...and prescribing treatment for each metabolite with an abnormal level". The response states that "applicant has found that a global analysis of a plurality of metabolites, in contrast to examination and treatment of specific,

individual metabolites and specific inborn errors of metabolism, results in more accurate diagnosis and treatment of chromosomal abnormalities, including Down Syndrome". The response argues that the Hoffmann et al reference "generally teaches a method for qualitative and quantitative determination of organic acids, aldehydes, and ketones in urine, plasma, or amniotic fluid samples that requires no deproteinization" and "fails to teach or suggest the identification of increased or decreased levels of a plurality of metabolites during a single procedure, and relative to a control profile, and the prescribing of appropriate cofactors or blocking of the appropriate enzymes". The response states that "Galjaard merely surveys a history of fetal diagnosis of inborn errors of metabolism", and that Galjaard "fails to teach, disclose, or suggest the identifying of increased or decreased levels of a plurality of metabolites during a single procedure in order to identify and treat chromosomal abnormalities".

These arguments have been thoroughly considered but are not convincing for the following reasons. First, it is noted that the present claims are not limited to methods for "characterizing" levels of metabolites "in an amniotic fluid sample"; rather, the claims merely require analysis of a sample of a "bodily fluid". Further, while applicant's arguments refer to a chromosomal abnormality "such as, e.g., Down Syndrome" and to a "global analysis of a plurality of metabolites" that result "in more accurate diagnosis and treatment of chromosomal abnormalities, including Down Syndrome", the claims are not limited to Down Syndrome or to "analysis" of a particular panel of metabolites whose levels were found to be altered in a Down Syndrome patient, but rather encompass analysis of any "plurality" of metabolite levels in a patient

with any type of chromosomal abnormality. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). With respect to applicants argument that the Hoffmann et al reference fails to teach identification of metabolite levels during "a single procedure" and the "prescribing" of cofactors or the blocking of enzymes, it is noted that Hoffmann et al's method does constitute a "single procedure" having multiple steps that includes comparison with control levels and analysis of differences, and that the present claims do not require the prescribing of cofactors or the blocking of enzymes, but merely require "prescribing a biochemical treatment for each respective metabolite having a different level when compared with the normal level of that metabolite". It is again noted that Hoffmann et al do suggest modifying treatments in response to metabolic profiles (p. 587). Further, the present claims encompass methods comprising steps of "generating" and "analyzing" that do not result in the detection of any metabolic abnormalities; the final process step of "prescribing" is only practiced if levels that differ from a normal level are detected. With respect to the Galjaard reference, it is noted that the Galjaard reference was not cited for a teaching of "identifying of increased or decreased levels of a plurality of metabolites during a single procedure", but for its teaching that one may diagnose a variety of genetic metabolic diseases in a fetus by "biochemical analysis of amniotic fluid supernatant", as discussed in the Office action of paper no. 5 (see Galjaard, p. 549-551). Additionally, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413,

208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). With respect to claim 5, it is noted that the claim recites a series of 'prescribing" steps that are only performed "if" abnormal levels of particular metabolites are detected. As the claims as written do not require that any of these abnormalities actually be detected, the combined references of Hoffmann et al and Galjaard are sufficient to suggest the method of the claim.

The combined references of Hoffmann et al and Galjaard suggest all the limitations of present claims 1-3 and 6, and therefore this rejection is maintained.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday from 7:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at 703/308-1152. The fax phone number for the Technology Center where this application or proceeding is assigned is 703/305-3014 or 305-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana Johannsen

June 18, 2001

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER